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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 29915/00281FUS

	Application Number	Filed
	10/801,487	March 16, 2004
	First Named Inventor: Riqiang Yan et al.	
	Art Unit: 1639	Examiner: J. S. Lundgren

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 38,153
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

Signature

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September 11, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: September 11, 2007 Signature:  (David A. Gass)

REMARKS TO ACCOMPANY PRE-APEAL BREIF REQUEST

I. It was improper to maintain the provisional double patenting rejection because the claims are not coextensive with pending claims in related applications.

In the first office action, claims were rejected under §101 as allegedly coextensive in scope with pending claims in related applications. Independent claim 84 and other claims were narrowed by amendment filed on December 5, 2006, rendering moot the double patenting rejection. It should have been withdrawn in the final action. No nonstatutory double patenting rejections were made and Applicants request that such rejections be held in abeyance until claims are found otherwise allowable.

II. Deficiencies in the written description rejection.

Although the current claims are directed to a method, the written description rejection focuses on the genus of novel substrate peptides that are used in the method. (The Examiner appears to accept that there is adequate support for the methods steps *per se*, apart from the genus of substrate peptides.) Hence, the arguments here are limited to written description of the peptide substrates.

A The specification shows that the Applicants were in possession of the invention at the time of filing.

At page 10 of the final action the Examiner observes that Table 6 in the specification effectively discloses 9,870,400 substrate permutations, and incorrectly asserts that the Applicants "selectively trimmed their own genus down by an order of 10^6" based on what others have discovered.

The Applicants were in possession of the claimed invention at the time of filing. First, Table 6 and the comparable text at p. 5 of the application provide explicit basis for claiming *every single one* of the 9,870,400 peptide permutations defined by the table, individually or as any subgenus. A person provided only with page 30 of the application (which contains Table 6) could write the amino acid sequence of each one of these 9,870,400 different peptides. The Applicants' depiction of the 9,870,400 peptides in Table 6 satisfies the "conciseness" requirement of 35 USC §112, ¶1 better than listing them individually, but the table still provides basis for claiming every peptide individually. The Applicants explicitly state at the bottom of page 13 of the application that they contemplate all embodiments of the invention narrower in scope in any way than the variations specifically mentioned in the summary, thereby providing additional support for subgenus or species

claims. If, after the filing date, others "discovered" *substrate properties* of some of the Applicants' peptides, as suggested by the Examiner, these "others" have done nothing more than copy or independently confirm substrate properties of peptides first described by the current Applicants. The Examiner is wrong to allege that the reverse is true.

In addition to the foregoing, the specification contains explicit support for the subgenus of the current claims. First, the original and current independent claims define with particularity two residues on either side of the scissile bond, namely positions P_2, P_1, P_1' and P_2'. (Dependent claims in the original and current claim set further define surrounding positions, *e.g.*, P_4, P_3, P_3', and/or P_4'.) Thus, the Applicants did not engage in post-filing "trimming" by focusing on these four residues, rather than those more distant from the scissile bond and less important to cleavage. The number of permutations in Table 6 *for the four residues in question* is only 2940 (10x6x7x7), not 9,870,400, as asserted by the Examiner. The allegation of 1/1,000,000 "trimming" is plainly incorrect.

The specification also provides explicit support for the subgenus of nine peptide core sequences defined by current claim 84: a peptide comprising the sequence P_2P_1-$P_1{\cdot}P_2'$ wherein P_2 is N; P_1 is Y, L and F; P_1' is E, A or D; and P_2' is V. The specification teaches that:

> In the peptides of the present invention that were effective Hu-Asp2 [human aspartyl protease] substrates, Tyr/Phe [Y/F] and L were the most abundant amino acids at the P_1 site; Asn [N] appeared several times at the P_2 site; Glu, Asp, and Ala [E, D, and A], were prominent in the P_1'; Val [V] occurred frequently in the P_2'... [Page 19, paragraph 2]

Thus, the application clearly and explicitly contemplates the specific peptide subgenus recited in the claims.

B The Examiner incorrectly asserts that the claims encompass a significant number of inoperative substrates.

At page 11 the Examiner asserts that the current scope of the claims does not meet the standard set forth in *Atlas Powder*, an opinion in which the Federal Circuit observed that it is not a function of the claims to specifically exclude possible inoperative embodiments, the question of undue experimentation depending upon whether the number of inoperative embodiments becomes significant. The Examiner specifically asserts that the application fails to support claims concerning substrate peptides wherein P_1 is F. (Final action p. 6.)

First, even if the claims encompass almost 10 million peptide permutations, as alleged by the Examiner, this genus is not large in the context of high throughput screening techniques that were common in the fields of chemistry and molecular biology at the time the application was filed. Indeed, Patent Office precedent for cases involving biological molecules teach that a single disclosed species is often an adequate description of a large genus of polypeptide or polynucleotide molecules defined by appropriate structural limitations and an activity limitation. The Patent Office routinely allows claims that recite genera of biological macromolecules many orders of magnitude larger than any genus at issue here (whether nine or 9,870,400), based on fewer working examples than are present here.

Second, claim 84 explicitly specifies that "the substrate is cleaved between P_1 and $P_{1'}$ by [the protease]." This activity limitation for the peptide is consistent with guidance for claiming that is found in the PTO's Written Description Training Materials, and it assures that the claim encompasses zero inoperative embodiments. (The application also teaches activity assays that can be used to confirm cleavable substrates through routine screening.)

Third, the record contains substantial evidence that most of the nine core sequences (five of the nine) recited in the claims are cleaved by the protease, and no evidence that any of the core sequences cannot be cleaved. According to the United States Patent and Trademark Office Revised Interim Written Description Guidelines, the specification provides an adequate written description of a genus if a *representative* number of species are implicitly or explicitly disclosed. Clearly, all members of the claimed genus are explicitly disclosed in the application. Furthermore, the application exemplifies the functionality of a representative number of the species in the genus. Specifically, the application demonstrates that five peptides within the claimed genus SEQ ID NO:5 (NYEV), SEQ ID NO:133 (NLEV), SEQ ID NO:7 (NYAV), SEQ ID NO:46 (NYDV) and SEQ ID NO:47 (NLAV) are cleaved by an aspartyl protease. The Examiner alleges that the definition of P_1 as F is not adequately supported because it is not specifically exemplified. However, a peptide comprising F at the P_1 position (SEQ ID NO:118) was tested and found to be cleaved by aspartyl protease, albeit less efficiently than the highly active Swedish mutant sequence (see text spanning pages 15-16). Furthermore, a number of different peptides were tested wherein P_1 is Y, an amino acid residue that is structurally similar to F and differs from F by only a single hydroxyl group, and each of these peptides were shown to be functional (*e.g.*, SEQ ID NOs:43, 5, 7 and 46).

Thus, the skilled artisan would clearly recognize that the application supported the claimed genus of peptides including peptides wherein F is in the P_1 position.

The references cited by the Examiner further support the sufficiency of the teachings in the application. Specifically, in Shi *et al.* (2005) three additional substrates of the claimed genus (NFDV, NFEV and NLDV) are demonstrated to be cleaved more efficiently than wild type APP, one of which is cleaved at 10 fold greater efficiency. In particular, Shi demonstrates that peptides comprising an F at the P_1 position are cleaved very efficiently (see, *e.g.,* figure 2 on page 143). See also U.S. Patent No. 7,132,401 (Table 3), PCT Publication No. WO 02/094985 (page 41, lines 19-25) and PCT Publication No. WO 03/072041. Based on the evidence of record that eight of the nine peptide sequences of the claim are cleaved, it was clear error to maintain the written description rejection.

C The Examiner erred by alleging that literature supported a rejection.

To allegedly demonstrate an insufficiency in the teachings of the application, the Examiner cited Gruninger-Leitch *et al.* (2002), Majer *et al.* (1997), Sauder *et al.* 2000, Shi *et al.* (2005) and Tomasselli *et al.* (2003), and argued that these references show peptide substrates with a variety of substitutions show *decreased* cleavage by aspartic proteases and thereby demonstrate that the genus of substrate peptides are insufficiently defined in the instant application. However, the only substrate that satisfies the structural limitation of claim 84 that is demonstrated as inoperative is one mutant APP sequence (NFAV) from Shi (page 142, Table 2), and even this substrate falls outside the claims if it fails to satisfy the functional limitation of the claim. While some substrates of the cited references may be non-optimal, the references do not characterize any other substrate within the claims as inoperative. Moreover, it is not a function of the claims to specifically exclude possible inoperative embodiments. The Federal Circuit has stated:

> Where there are a myriad of operative combinations, the inclusion of a few that are not operative need not invalidate a patent. The patent's claims can be construed to exclude those inoperative combinations. Including such inoperative combinations within the scope of a claim does not constitute invalidating "overclaiming." *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.,* 588 F. Supp. 1455, 221 U.S.P.Q. 426 (Tex. 1983).

In this case the claims explicitly exclude any inoperative embodiments. Nonetheless, a single inoperative peptide sequence amongst the 5 functional substrates demonstrated in the instant application and 3 further operative substrates confirmed by Shi do

not constitute a significant number of inoperative embodiments. Thus, none of the references cited by the Examiner support the instant rejection.

The Examiner pointed to Table 1 of Gruninger-Leitch *et al.* to illustrate that a single change to the amino acid sequence of a substrate may result in a decrease in cleavage activity. However, all substrates set out in Table 1 of Gruninger-Leitch *et al.*, that were designed to be cleaved by the β-secretase enzyme, exhibited some activity. The inactive substrates were either designed to be cleaved by α-secretase or renin, and are not encompassed by the claims.

The Examiner pointed to examples in Gruninger-Leitch *et al.* which demonstrate that a single point mutation at the $P_{1'}$ or P_4 of the Swedish mutant cleavage site results in a drop in the rate of cleavage. However, none of the substrate peptides cited in these arguments are encompassed by the claimed genus (*i.e.*, cited peptides comprise A at the $P_{2'}$ position). Also, it is unfair to assert that substrates cleaved at a lower efficiency do not support the claimed genus when this measured efficiency was determined by a comparison of cleavage of the highly efficient "Swedish mutation" substrate. Even the wild-type substrate has only 9% cleavage compared to the Swedish mutation, yet it can be used in assays. These cited documents further support the claimed genus with observations such as, "[t]he data presented above also indicates that BACE can accept a wide variety of peptidic substrate." (Gruninger-Leitch *et al.* page 4692, bottom of right column.) and "[t]he results of the present investigation further indicate that BACE1 can accept a wide variety of amino acid residues at the β-scissile-bond of its substrate both in vitro and in cells." (Shi *et al.* page 146, left column). The Applicants impeach the art cited by the Examiner in greater detail at pages 11-14 of the amendment filed in December, 2006.

The claims read on substrates that are longer than 6 amino acids. However, the Applicants teach in the application (as recognized by the Examiner and nicely explained in their later-published paper by Tomasselli *et al.*) that additional amino acids appears to enhance the reactivity of β-secretase toward the recognition site. (*See* Tomasselli at p. 1009 and Table 1, for example.)

III. Conclusion

For all of these reasons, the rejections were improper and should be withdrawn.